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ABSTRACT

Evidence today indicates that the causes of mental retardation are biological, psychological, and social in origin and that a combination of these causes frequently occur in a single individual. Mental retardation is identified clinically by the presence of several signs that include, but are not limited to, a significant impairment of intelligence and a concurrent deficit in adaptive behavior. This monograph presents a report on the current state of knowledge about mental retardation. Research progress and objectives in the biomedical, behavioral, and social aspects of this handicap are discussed. Priority areas for future research are identified, including needs for biomedical research in biology, anatomy, chemistry, pharmacology, and physiology. A need is seen also for research in genetics and inborn errors of metabolism. Behavioral and social sciences research is called for in the areas of prevention of mental retardation, enhancing thinking and learning in retarded individuals, amelioration of the effects of mental retardation, and alternatives to institutionalization of retarded persons. A bibliography of 45 references is appended. (JD)

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Mental Retardation

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Table of Contents

		Page
Acknowledgments		1
I.	Introduction	1
II.	Current State of Knowledge: Research Progress and Objectives	3
	Biomedical Aspects	3
	Normal and Abnormal Brain Maturation: Problems and Perspectives	3
	Genetics and Metabolism	18
	Behavioral and Social Aspects	21
	Plasticity of Measured Intelligence	22
	Developmental Processes	23
	Memory	24
	Attention	24
	Learning	25
	Language	26
	Social and Personality Development	27
	Biology-Behavior Interaction	28
	Toward a New Definition of Mental Retardation	28
	Important Questions	30
	Life Span and Life Transition	30
	Cognitive Training	32
	Retardation and the Family	33
	Ecology	33
	Biology and Behavior	34
	Training in Specific Skills	34
III.	Priority Areas for Research	35
	Biomedical Research	35
	Neurobiology and Neuroanatomy	35
	Neurochemistry and Neuropharmacology	36
	Neurophysiology	36

Table of Contents (Continued)

Genetics and Inborn Errors of Metabolism 37
Behavioral and Social Sciences Research . . . 37
Prevention of Mental Retardation Due to Unknown Causes 37
Enhancing Thinking and Learning in Retarded Individuals 38
Amelioration of the Effects of Mental Retardation 38
Alternatives to Institutionalization of Retarded Persons 38

References 39

Mental Retardation

I. Introduction

Evidence today indicates that the causes of mental retardation are biological, psychological, and social in origin and that they occur frequently in combination in a single individual. Genetic factors, metabolic disorders, and prematurity or other disturbances during pregnancy are a few of its biological determinants, but infection or injury at birth or in early childhood may also underlie mental retardation. In addition, lack of stimulation, inadequate educational opportunities, and generally deprived living conditions may be causal or contributory factors. Whether such factors modify normal developmental processes or cause aberrant neurogenetic programs is not at all clear. The moderate and more severe conditions of retardation most frequently result from disorders or insults that can usually be traced to faulty genes, infections, accidents, diseases, and disorders that cause brain damage. Knowledge is needed from almost every branch of science in order to understand the interaction of these elements in the development and behavior of children and adults.

Mental retardation is identified clinically by the presence of several signs that include, but are not limited to, a significant impairment of intelligence and a concurrent deficit in adaptive behavior. Typically, these impairments occur before age 18. The identification of mental retardation through the years has reflected with varying degrees of emphasis a mix of two factors. Before the beginning of the mental testing movement, the primary behavioral characteristic of those who were referred to as mentally retarded was inadequate social adaptation. With the rise of the mental testing movement, specifically with regard to intelligence testing, a greater reliance has been placed on measured intelligence as the primary characteristic in

defining mental retardation. The term intelligence was used to refer to the ability of the individual to master verbal, visual, and mathematical symbol systems, and the concept of intelligence itself became defined by the instruments that purported to measure it. In 1922, for instance, 23,000 students in public schools were enrolled in special education programs for the mentally retarded. In contrast, there were 87,000 such enrollments in 1948[1] and 1,350,000 in 1975.[2] Social systems, such as diagnostic clinics, public schools, and other service agencies, have created standards of definition that vary on the basis of different perceptions of individual and societal needs.

Because of the ambiguity of definitions, different estimates have been made of the prevalence of mental retardation. The traditional method, based upon the normal distribution of intelligence test scores, places the number of mentally retarded in 1979 at an estimated 6.6 million Americans, or 3 percent of the general population.[3] Some authorities, employing more exclusive clinical criteria, estimate the frequency at 1 to 2 percent of the population, or between 2.2 and 4.4 million persons. Still other authorities expand the estimated number of retarded individuals by including the less severely affected--that is, persons with IQ's up to 80 and with problems in social adaptation. The most difficult cases to classify are those that exist at the boundaries. These consist of individuals who may exhibit subnormal intellectual functioning but who are socially adept. Moreover, there may be those who score below normal IQ and who, because of specific or informal training, are able to function successfully at a reduced level in the mainstream of society.

Programs for the mentally retarded vary with the cause, type, and degree of retardation. They involve, either directly or indirectly, most agencies of government at the Federal, state, and community levels. The cost of these programs is staggering. Total public expenditures for support of mental retardation programs in FY 1979, for instance, approximated $10 billion. The Department of Health and Human Services (DHHS) anticipated spending an estimated $1.9 billion on the problem in FY 1980.[4] State and local governments were expected to expend four times that amount. Such funds are used for a wide range of programs, including prevention, provision for basic needs, residential and community care, health, education and habilitation, and employment.

In 1970, approximately 270,000 mentally retarded persons were cared for in public residential care institutions. By 1980, this figure was reduced to about 139,000 under the impetus of a national program of deinstitutionalization in which much of the institutionalized population was shifted to community care facilities. The estimated costs

for the care of these persons are $3 billion per year. Current estimates place 62,397 mentally retarded persons in this kind of care, for which community residential facilities reimbursements, a portion of total care costs, approximate $1 billion a year.[3]

The foregoing sampling provides an incomplete picture. The number of retarded children and those at risk for becoming retarded are probably underreported. In addition, many retarded persons merge with the population at large upon leaving structured school programs. The deficits of the developmental years often continue to reduce their employability, impair their social adjustment, and effect a dependency requiring economic and social support.

II. Current State of Knowledge: Research Progress and Objectives

Biomedical Aspects

Much of the effort to date in the biomedical aspects of mental retardation research has been directed toward the identification of specific causative factors, such as hypothyroidism, genetic abnormalities, phenylketonuria (PKU), and other inborn errors of metabolism.[5] It is of great importance, for instance, that phenylketonuria be identified in the neonate and that dietary measures be taken to prevent significant mental impairment as a result of this metabolic error. The fact that enzyme deficiencies of neuronal storage disorders such as Tay-Sachs disease can be identified antenatally or that thyroid replacement therapy, if initiated in time, can prevent mental deficiency underscores the remarkable accomplishments of past research.

What must be addressed now is the fundamental question of mechanism[6,7] at cellular, neurointegrative, and sociobehavioral levels of organization. This is the major objective of the research programs summarized here. The focus is on high-priority areas of inquiry that can be productively explored in the next 5 years with realistic expectations for success.

Normal and Abnormal Brain Maturation: Problems and Perspectives

During the course of human brain development, neurons are differentiated, become organized into different systems,

and make appropriate functional connections with other neurons, sensory organs, and muscles. One of the truly awesome biological statistics is that during human brain maturation 200 billion neurons will be generated and make synaptic connections such that each neuron will receive 10,000 to 200,000 synaptic connections and will make the same or more synapses with other neurons, including some with itself.

The process of brain development begins in the earliest stages of embryonic life and extends well into the second postnatal decade. With the exception of the cerebellum, a structure concerned largely with coordination of movement, the brain probably acquires its full complement of neurons in the human infant prior to birth and perhaps as early as the beginning of the last trimester of gestation.[8] While excellent data are available on the time of origin of many of the neurons in the monkey brain, nothing is known concerning the schedules of generation or the numbers of neurons produced in the embryonic and early fetal stages of human brain development. Since one of the primary requirements for normal brain function is a sufficient number of neurons (whatever this number may be), it follows that identification of the genetic and epigenetic factors regulating the formation of the "correct" number of neurons is of critical importance. One approach to this problem must be sought in the pursuit of in vivo laboratory animal and cell culture studies of developing neuron systems to define regulatory factors of neurogenesis and process formation in early differentiating neurons.

While neurons constitute the fundamental information processing unit of the brain, they are outnumbered by the supporting cells or glia, which play several crucial biological roles in facilitating neuronal operations and processes.[9] In the mature brain, glia far outnumber neurons, but the period of maximal glial proliferation occurs somewhat later than the growth spurt period for neurons. What factors determine the relative numbers of glia and neurons and the extent to which early mechanisms of intercellular communication play a role in signaling functions in glia-glial and neuron-glial relations are unknown.

Neurochemists and immunologists have made great progress in identifying "marker" molecules in the plasma membranes of isolated neurons and glia, which suggest a number of biochemical mechanisms underlying cell specificity.[10] These studies have been greatly aided by the use of dissociated cell systems, neuroblastoma and hybrid cells, and monoclonal antibodies to specific cell surface antigens. These studies are in the earliest stages of development, but they hold great promise for answering some of the most important questions in developmental neurobiology--namely, how does a neuron "tell" the difference between itself and

other neurons, how does it recognize neurons it wants to contact while avoiding others, and finally how do neurons and glia know when to turn on metabolic reactions that unite them in functional units?

Neurons once formed must sometimes travel or migrate relatively great distances in the developing brain to reach the correct addresses in the neuronal subsystem for which they were originally specified by genetic programs. Research over the past decade has provided clues to at least two mechanisms of neuronal migration. Newly formed neurons at early stages in embryonic development produce long processes that arise from the ends of their cell bodies. One process anchors itself to the lining of the primitive ventricular cavity immediately subjacent to the germinative layers, while the other process grows into the wall of the developing pallium (primitive cerebrum) until it makes contact with the outer surface membrane. In this way primary polar processes serve to anchor the primitive neuron to a particular site. There follows a process whereby the cell body with its nucleus migrates intracellularly to a position remote from its place of origin.

Intracellular migration of the cell body can also occur by movement of the cell body away from the early processes it emits. Both forms of neuronal migration must involve complex, temporospatial regulation of intraneuronal cytoskeletal elements that aid in the extension and directed growth of processes. Additionally, there must be continued incorporation of newly synthesized surface membrane constituents during the growth of processes. Once the correct address has been attained, extended processes must be reabsorbed or transformed into other elements such as dendrites or axons during the subsequent phase of neuronal differentiation.

The phenomenon of neurite or process formation in primitive neurons introduces another set of critical neurobiological issues. Process formation and extension are events requiring assembly of microtubules, a variety of filamentous structures and other components that constitute the cytonet and cytoskeleton of neurons. The production of microtubule proteins, their assembly and disassembly, and the incorporation of plasma membrane constituents at the growing ends (growth cones) of developing processes are problems of fundamental importance that will require considerable attention. This point will be given further emphasis below.

At a later stage of development, newly formed neurons undergo "free" migration to attain their correct position in the brain.[8] Neurons destined for the cerebral cortex are aided in the migratory process by the presence of long radial processes of specialized glial cells that span the

thickness of the primitive pallium. The phenomenon encompasses a variety of progressively more complex problems. It is clear that the time a neuron is formed is a determinant of the position the neuron will eventually attain in the cerebral cortex. Time of origin is also related to neuron typology--that is, what kind of neuron the differentiated element will be. The relationship between the neuron and glial cell must be specified in some way, but how?

Recent research has provided evidence that the plasma membrane of neurons is a mosaic of charged macromolecules consisting of glycolipids, glycoproteins, and glycoaminoglycans.[9,10] Are the electrochemical signals resulting from different configurations of charged surface macromolecules matched by the complementary macromolecules associated with different but related cells? What factors guide the neuron to its proper location? For many years it has been argued that gradients of "chemical" signals in the external milieu of developing processes can influence directed growth by inducing the cytoskeletal system of the neuron to extend processes in the direction of increasing potency of the "signal." Alternatively it has been argued that a substrate of nonneuronal cells is first formed for "pioneering" processes, and additional processes follow the leading elements. In the case of neurons migrating in close relationship to glial radial fibers, what are the chemical signals exchanged during the "contact guidance" mechanism? Since faulty migration of neurons related to the loss of effective guidance by specialized glial cells is associated with disorganization and even neuronal attrition in subsystems involved in complex cortical functions, studies of neuronal migration and mobility should continue to be encouraged and supported.

The orderly development of some parts of the brain and spinal cord depends not only upon the production and proper location of a specified number of neurons but also on the elimination of a variable proportion of neurons during and after the establishment of much of the circuitry of the nervous system.[9,11] In recent years, much evidence has accumulated to the effect that programmed neuronal death is a prominent feature of developmental processes. Why are more neurons generated in some sites than appear necessary to carry out a particular function? What factors concerning the relations of these neurons with their target sites or with the activity they exhibit determine neuronal death? Do some neurons in cerebral cortex exhibit early cell death because of similar determinants? Answers to these questions are clearly within the scope of current neurobiological research efforts and should continue to be sought.

For the most part the processes of neuronal proliferation and migration are early developmental events in the

human brain usually occupying the first half of gestation. Beyond the 20th week, neuronal differentiation--that is, the development of dendrites and axons, and the formation of synaptic connections--dominates the developmental process. The extensive dendritic systems of pyramidal neurons of the cerebral cortex will eventually serve as receptor surfaces for a variable synaptic input from other neurons. In the human infant, dendritic branching patterns of most types of neurons in the cerebral cortex are established by the time of birth. Increase in segment length and terminal branching continue throughout the first and second year, and perhaps longer.[7,12] Since dendrites of pyramidal neurons, the predominant cell type of the cerebral cortex, provide 95 percent of the available membrane surface area for synaptic contacts, it follows that factors which influence dendritic growth and development will significantly modify the functional activity of the cerebral cortex. Overt alterations in dendritic branching patterns and dendrite/soma volume ratios have been documented in immature laboratory animals in experimental hypothyroidism, phenylalanine loading, lead intoxication, fetal alcoholism, malnutrition, corticosteroid administration, X-irradiation, various genetic mutations, and environmental deprivation.[5,13] These perturbations also exert a profound impact on the number, morphology, and distribution of dendritic spines, which are the small protuberances of dendrites that serve as postsynaptic targets for presynaptic axons of neighboring and distant neurons.

Observations reported in recent years point to the vulnerability of dendritic spines in a wide variety of neurobehavioral developmental disorders associated with mental retardation.[14] What must be understood is the fundamental mechanism regulating dendritic spine formation. Dendritic spines with postsynaptic membrane particles indicative of receptor-like elements can exist in the absence of presynaptic processes. But how does the loss of previously established synapses involving dendritic spines alter spine morphology and function? One of the striking observations relating to dendritic spine morphology has been made in examination of cortical neurons in a number of cases of developmental failure with profound mental retardation.[12,14] In these cases the major abnormality involves structural features of dendritic spines, many of which retain fetal-like characteristics. Such observations suggest for examination the full range of processes governing dendritic spine maturation and the establishment of spine synapses.

A closely related problem has been disclosed in the recent discovery that profoundly retarded infants and children whose cortical neurons exhibit abnormal dendritic spines also show varicose transformations in dendrites that take on a "string-of-beads" appearance beginning with the most distal dendrite segments. Correlated electron-microscope

studies of these varicose dendrites disclose a prominent disarray of microtubules with swirls of these elements in the varicosities. Evidently a disorganization in the mechanisms of alignment parallel to the long axis of dendrites may be an important factor in the genesis of the dendritic varicosity, with subsequent alteration in dendritic spines and the loss of integrative property of dendritic systems. This is the most likely explanation for progressive developmental failure. Again these observations point to elementary biological mechanisms involved in microtubule polymerization and depolymerization and the factors that could affect processes for regulating neuronal geometry and dendritic morphophysiological properties.

The problem of defining the fundamental mechanisms of neuron-neuron and neuron-glial recognition was noted above in relation to neuronal migration and process formation. This problem is, in fact, the central issue of developmental neurobiology and, for this reason alone, requires additional comments in respect to mechanisms of synaptogenesis.

When one considers the staggering number of correct synaptic relations that must be effected in the development of the competent brain, the problem of elucidating the rules and principles guiding the establishment of these synaptic connections in the normal mature brain is overwhelming. There are no definitive answers to the major enigma of neurobiology--that is, how do neurons make and maintain appropriate connections? Although there have been heuristically valuable speculations based for the most part on "chemoaffinity" theories of one kind or another as noted above,[9,11] the fundamental secrets of brain development remain unknown in this problem. Its solution will greatly facilitate an understanding of the impact of developmental perturbations on synaptogenesis.

Regulatory mechanisms in synapse formation and operation are being studied in a wide variety of biological preparations and even in some artificial membrane systems. It is now appreciated that the nature of the target sought by a presynaptic element defines not only the number of synapses but also the functional type of connections and the nature of the chemical transmitter that operates the synapse. More than a quarter of a century has passed since the first definitive nerve growth factor for the development of sympathetic ganglia was identified in salivary glands and other tissues. Since then, growth factors have been shown to play important roles in regulating the metabolic machinery for cell differentiation, neurite growth, transmitter synthesis, and synapse formation.

The vast amount of work in the field of "trophic" agents raises the question of whether there are specific

growth factors capable of influencing neuronal differentiation and synaptogenesis in the human cerebral cortex. In this connection, recent studies of neuronal storage diseases, in which morphological methods for demonstrating neurons in their entirety are employed, have revealed the presence of neuritic growth and secondary, but aberrant, dendritic differentiation on mature human cortical neurons laden with gangliosides and other complex metabolites.[12]

It is evident from these observations that neuronal storage disorders must be viewed as derangements of cell surface membrane regulation. What is more intriguing, however, is that findings of secondary dendritic growth and differentiation in neurons in these inborn errors of metabolism point to the role of gangliosides and probably other glycolipids and glycoproteins in the establishment of neuronal interrelations. It should be emphasized that neuronal storage diseases are invariably associated with mental retardation and, in many instances, progressive neurobehavioral deterioration and death. There is evidence to suggest that intracellular accumulation of storage material per se is not the primary factor that leads to neuronal dysfunction.[12] Hence, the mechanisms of neuronal geometry distortion, new neurite and synapse formation, and other factors that alter neuronal function in these metabolic disorders must be clarified.

Procedures for studying morphogenetic events at the light- and electron-microscope level are now sufficiently advanced to permit detailed analysis of immunofluorescent-labeled cell surface antigens, membrane particles, and a host of subcellular organelles related to neuronal and glial processes. There is, however, a paucity of data on the changing functional properties of immature neurons and their synaptic organizations, due in large part to inherent difficulties in obtaining viable preparations for in vivo studies at very early stages of ontogenesis. It must be emphasized that the basic business of the nervous system is information processing, and its currency is electrical signals of varying complexity. Such signals are generated across the plasma membrane and involve different ionic species and processes at different sites in dendrites, cell body, axon, and pre- and postsynaptic components of synapses.

The pioneering studies of the early 1950s on the ionic basis of the nerve impulse and postsynaptic potentials served to uncover a wealth of mechanisms by which excitable cells generate different electrical activities. Early views of the physiological basis of the nerve impulse based on sequential changes in sodium and potassium permeabilities controlled by variations in the electrical field across the membrane have now been expanded to include consideration of

gating mechanisms by which such fields open or close transmembrane ion channels. Many laboratories throughout the world are concerned with the problems of how different transmembrane ion channels are influenced by drugs, synaptic transmitter agents, and a host of other naturally occurring biologically active agents. The role of calcium in a variety of electrogenic, as well as secretory and metabolic, processes of neurons has been of special interest in view of the extent to which transmembrane, as well as intracellular, calcium ion kinetics determine transduction of sensory processes, the release of synaptic transmitter agents, and postsynaptic electrogenic and metabolic events triggered by activation of various cyclic nucleotides. Calcium has been implicated in the electrogenic responses of the growing tips of neurites of developing neurons, which suggests a major role of this cation in neurogenesis and synapse formation.[10]

Unfortunately, virtually nothing is known about the factors that regulate or determine the number and distribution of different ion channels sensitive to membrane voltage or chemical transmitters in developing neurons. Data obtained from mature neurons and single axons point to an unequal distribution of sodium and potassium channels on the cell body surface and at different sites in axons. Calcium channels are ordinarily concentrated at presynaptic terminals. Their presence, however, in the dendrites of certain classes of central neurons, including dendrites of Purkinje cells of the cerebellum, and pyramidal neurons of the hippocampus, an old cortical structure, is highly likely. Quite remarkably, the growth of dendrites of Purkinje cells is accompanied by the appearance of electrical responses that are dependent in part on calcium.[10]

While action potentials dependent upon sodium are normally found in the cell body and axons of Purkinje cells, dendrites make use of voltage-sensitive changes in calcium permeability to generate a significant proportion of their electrical signals. There is also good evidence, obtained in the past few years, that calcium spikes in dendrites of hippocampal pyramidal cells may underlie the extraordinary excitability of these cells. Slow inward currents caused by calcium can activate newly discovered potassium currents that can repolarize the neuron and prepare it for cyclic excitability surges. It is imperative that more information be obtained on developmental factors regulating membrane electrogenesis since it is evident that abnormalities in electrical signaling in neuronal subsystems can wreak havoc with normal synaptic transactions.

One clue that this kind of inquiry will yield important data relevant to basic mechanisms is the observation that, in early states of neuronal maturation, pyramidal neurons of the cerebral neocortex exhibit partial and full spikes in

dendrites whereas dendritic spikes are not normally observed in mature neurons. Development in this instance is apparently accompanied by a redistribution or loss of ion channels or other processes regulating impulse generation in dendrites of these cells. An intriguing problem in this regard is the extent to which the changing electrical properties of dendritic membrane are related to the ontogenesis of dendritic spines, spine synapses, and other synapses on the dendritic shaft.

It is now well established that at the developing nerve-muscle junction, there is a great change in the acetylcholine sensitivity of the muscle membrane surrounding the site at which the nerve makes synaptic contact with the muscle. Evidently receptors for the transmitter are diffusely distributed, but such receptors at a later stage of development are concentrated at the synapse. Injury to the nerve or muscle tendon, or inactivity, can result in a return of this diffuse chemosensitivity. Striking changes in dendritic excitability with retraction of synapses can also be observed in spinal motoneurons following damage to the axon. Do these alterations in membrane properties occur also in cortical neurons as a consequence of damage to synaptic pathways or functional inactivity?

To answer this question will require: new knowledge on the nature, turnover, and distribution of receptors and receptor-ionophores--that is, molecules controlling ion channels in the membrane--in different parts of the neuron; the identity and mode of action of chemical agents that bind to these receptors; and how they modify the actions of other drugs and transmitters on synaptic and nonsynaptic membrane. Such information will bring us closer to understanding how synapses are formed, influenced by neighboring synapses, and stabilized during development. This would be particularly pertinent information, since it has recently been shown in several developing systems that more synapses are formed initially by different axons than is necessary for a particular function. One hypothesis is that chemical information is exchanged between pre- and postsynaptic elements that selectively stabilize one type of connection at the expense of others. This important developmental process of "synapse sculpturing" must play a role in shaping the functional circuitry of the maturing brain.[19]

Much of the foregoing discussion of fundamental mechanisms in neuronal signaling has emphasized the role of neurosecretory processes--the release of chemical agents by neurons--in the overall functional activity of the brain. Since the synthesis, transport, release, postsynaptic action, and inactivation of chemical synaptic messengers are complex interacting events, it is little wonder that the study of identified and suspected synaptic transmitters or

modulators of neuronal activity has become a major biological "growth industry." There remains hope that mental deficiency may be ameliorated by administration of specific chemicals or drugs capable of improving cognitive functions.

There are encouraging signs that manipulation of the brain's chemical machinery may be a productive future strategy in the biomedical management of mental retardation. These signs have emerged from new knowledge that the brain manufactures, stores, and distributes a wide variety of chemical agents of potential importance as transmitters or synapse modulators.[15,16] That the brain, rather than the pituitary, is the Master Gland is now abundantly clear from findings that a score of peptide-releasing and release-inhibitory factors regulating pituitary hormones are located in neurons at the base of the brain in the hypothalamus. These neurons are in turn influenced by synaptic pathways whose neuron cell bodies and axons are rich in biogenic amines, amino acid transmitters, other peptides, and acetylcholine. In the past decade, the number of such suspected transmitter/modular agents has nearly quadrupled, with at least 30 distinct chemical entities considered "putative transmitters." These include such agents as norepinephrine, dopamine, serotonin, gamma-amino butyric acid (GABA), glutamate, aspartate, glycine, the enkephalins, β -endorphin neuro tensin, vasopressin, somatostatin, substance P, cholecystokinin, vasoactive intestinal peptide, and possibly a number of hypophysiotropic factors of hypothalamic origin.

The use of discrete microbiochemical techniques and parallel immunocytochemical and autoradiographic methods for detecting suspected transmitter/modulator agents has resulted in establishment of a new field of neuroanatomy involving the mapping of neuronal pathways and connections by biochemical and pharmacological probes. These new methods, which also make use of the fact that neurons can take up precursor or marker molecules and thereby "light up" different pathways, have resulted in the discovery of brain circuits that could not be visualized (or imagined) previously. The past decade of exciting discoveries promises to be surpassed by the prospects of the next decade as neuroscientists focus on the biochemical pharmacology of the brain. What findings are likely to impact upon research efforts in mental retardation? A few examples follow.

It is known that the biogenic amine pathways from the brain stem are among the earliest to invade the developing forebrain and primitive cerebral cortex. How do these newly discovered systems influence cortical development? Do the transmitters released by biogenic amine pathways produce effects that are fundamentally different from the classical effects of transmitters such as acetylcholine at the neuromuscular junction? What role do these amines play in pro-

ducing long-term changes in synaptic activities at different stages of development?

Certain biogenic amines have been implicated in mechanisms of behavioral modification, particularly in animals with relatively simple nervous systems whose behaviors can be studied in precise morphophysiological detail. For example, sensitization is a process whereby an animal learns to increase a given response to novel (or injurious) stimuli. It has been shown at a cellular level that sensitization involves the action of a biogenic amine, serotonin, which serves to increase cyclic adenosine monophosphate (AMP), which in turn increases calcium influx and thereby enhances transmitter release at the sensitized synapse. These findings, which begin to relate overt specific behaviors to molecular events at the synapse, raise questions as to the role of biogenic amines, peptides, and other putative transmitters in the most complex operations of the human brain. A particularly surprising finding of recent years is that vasopressin, a posterior pituitary peptide of hypothalamic origin with well-defined actions on the kidney, may be implicated in a number of complex behavioral and regulatory effects, such as thermoregulation, by direct action on neuronal systems of the brain.

It has been known for many years that, although much of the neuronal circuitry of the brain is established via genetic instructions, the use to which this circuitry is put, as well as the disuse (or abuse) it suffers, can markedly alter the normal functional and, in some instances, the structural integrity, of the circuitry.[9,11,17] The most outstanding example of this is seen in the visual system, in which depriving the brain of visual input from one eye early in development reduces the number of cortical neurons that receive input from both eyes when animals are tested sometime after the period of deprivation. Pharmacological manipulations of the biogenic amine innervation of the visual cortex during the deprivation period have been reported to influence markedly and even prevent the effects of disuse, and they suggest that such pathways can modulate trophic interactions between competing synaptic pathways. Do the functional changes in synaptic efficacy in developing cerebral cortex, brought about by variations in sensory input in the laboratory animal, bear upon the issue of functional retardation in the socially and educationally disadvantaged child? Only a great deal of additional research at all levels of neuronal organization in studies aimed at defining mechanisms of functional validation of developing synaptic pathways will provide an answer to this intriguing question.

A final point of the possible relevance of transmitter agents to mental retardation research arises from recent

studies on the relationship of dietary factors to amino acid precursors of amine transmitters in the brain. Evidently blood and brain levels of two important biogenic amine precursors, tyrosine and tryptophan, can be significantly manipulated by diet. Choline, a precursor of acetylcholine, another important brain transmitter, can also be modified by dietary intake. Since acetylcholine and the biogenic amines are believed to be important in motivational systems and in learning and memory processes, it is not unlikely that deficits in these higher nervous functions could be due to or influenced by the availability of transmitter precursors. Further research along these lines, in addition to the studies required on developmental mechanisms of synthesis, storage, release, and synaptic actions of transmitter modular agents, are of central importance in mental retardation research.

The final stage in the development of the competent brain is the transformation of immature, slowly conducting pathways to high-speed conductile systems in accordance with specific requirements for rapid input-output information processing. This development is accomplished by proliferation of oligodendroglia and their activation to produce the insulating myelin that ensheaths axons except at bare sites called "nodes of Ranvier" at which sodium and potassium channels are concentrated. At myelinated segments between these nodes, there is little or no current flow; hence, the conducted impulse speedily "jumps" from node to node. The study of myelin, with its complex proteins, lipids, glycoproteins, and glycolipids, is still a major problem whose complexity constantly increases.

Myelination is known to be delayed or disorganized by a host of factors including malnutrition, hypothyroidism, and inborn errors of metabolism, all of which are associated with mental retardation.[5] It is now strongly suspected that axons must engage in some sophisticated signal interaction with oligodendroglia for the latter elements to wrap extended portions of their cytoplasm around a number of different axons. What are these signals and how are they regulated? What mechanisms control the formation of nodal membrane in the axon with its high density of transmembrane ion channels? These questions, along with previous issues concerning the role of astroglia in the production of radial fibers for aiding neuronal migration, implicate glia in some of the fundamental mechanisms of brain maturation and function. It would be difficult to envision a developmental disorder leading to severe mental retardation that did not impact upon the biological integrity of glial cells.

At this juncture in mental retardation research, it is appropriate to shift the focus from basic membrane, cellular, and synaptic processes to the wider purview of aggre-

gate neuronal operations distributed in different synaptic organizations. Despite intensive study, the problems of defining the morphophysiological substrate of sensation, perception, or the mechanism underlying even the simplest volitional movements remain unresolved. There is great need to explore further the sensory transduction process at different types of receptors, particularly for audition and vision, and to employ new anatomical marker techniques for identifying neurons at various sites. Multiple microelectrode recording techniques for simultaneous registration of electrical signals and on-line computer-assisted methods of data analysis must be further refined to allow for the investigation of event-related activities at several sites. In this way, clues may be forthcoming on the significance of distributed activities in different subsystems involved in particular sensorimotor functions as well as memory and learning.

Computer-assisted methods of recording and analyzing evoked potentials in human subjects permit detection of potential changes localized to relatively small portions of the brain. In several studies, signals have been recorded that relate to language functions in auditory and visual modalities in normal and perceptually impaired subjects. Attempts are also being made to use these techniques for objective neurophysiological measures of behavioral competency as an adjunct to neurological and behavioral assessment of preterm infants at risk for mental retardation. Continued exploration of these tactics for early detection of neurobehavioral deficits may permit development of intervention strategies for prevention of later cognitive disabilities in high-risk preterm infants.

While much important research on the development of normal and aberrant perceptual and cognitive processes in the human infant can be anticipated with the sophisticated computer-based electrophysiological and behavioral techniques noted above, a wide range of more basic issues concerning the organization of the cerebral cortex and its related structures requires continuing consideration. Genetic factors in brain organization can be profitably examined in morphophysiological, biochemical, and immunobiological studies of animal mutants. These studies have already yielded a wealth of data on determinants of cellular architecture and organization in different types of cortex and other laminar structures and can be expected to be continuously productive. Other animal models of metabolic disorders that mirror in all respects inherited deficiencies in human infants should also be utilized more widely. For example, feline G_{M1}- and G_{M2}-gangliosidosis is a superb model of human storage diseases such as Tay-Sachs disease and promises to provide basic data on the mechanism of brain dysfunctions in a wide range of neuron storage diseases.

In the past decade, great impetus has been given to the analysis of genetic mechanisms regulating behavioral processes as a result of intensive biochemical and morphophysiological studies of specific behavioral deficits in paramecia, nematodes, leeches, molluscs, fruitflies and other insects, and mice. Behavioral genetics is a rapidly expanding area of neurobiological inquiry that will continue to yield critical data on the interaction of genetic and epigenetic factors in the regulation and expression of simple as well as complex behaviors.

Models of abnormal brain function have also been developed over several decades with various surgical or chemical techniques for the production of discrete lesions. Much information on the response of the immature brain to the loss of basal ganglia structures and related systems has been obtained in recent studies employing both surgical and neurotoxin techniques. The use of neurotoxins including kainic acid and other toxic analogs of putative transmitter agents to eliminate specific pharmacologically distinct components of complex pathways should provide critical data on the contributions of different systems to overt behavioral abnormalities. Several heuristic models of neurobehavioral "retardation" in rats with selective neurotoxin-induced lesions of norepinephrine, dopamine, and serotonin pathways produced in the neonatal period are already yielding data on possible mechanisms of neurobehavioral retardation.

This brief survey of problems and perspectives in mental retardation research would be incomplete without consideration of the most intriguing question in contemporary neuroscience: Is the brain modifiable? The immediate response to the question, of course, is--whose brain, and what is meant by modifiability?[16] Issues here are frequently confounded in "specificity/plasticity," or more commonly, "nature/nurture" polemics. That the brain is functionally modifiable seems self-evident from even a casual consideration of cognitive development in infancy and childhood. An early period of plasticity in the establishment of the functional and structural integrity of the visual system in cat and monkey has long been established. An imbalance in visual input in subhuman primates up to a certain period postnatally, approximately 3 months, results in significant morphophysiological changes in neurons at subcortical and cortical sites. Evidently the monkey's visual system undergoes hardwiring after this period and is no longer significantly modifiable by sensory deprivation thereafter. While early monocular visual deprivation produces profound deficits in binocularly driven neurons of visual cortex, reverse suture before the end of the critical period leads to morphophysiological reactivation of cortical synaptic pathways driven by the previously deprived eye. This reactivation is indicative of a remarkable degree of

modifiability of initially genetically programmed neuronal circuitry in the primate brain in the early postnatal period.[18] A host of other studies has demonstrated varying degrees of modifiability of developing as well as of some mature systems in the mammalian brain.[19] One may envision a series of discrete critical periods for different hard wired functions, such as initial visual and auditory information processing and perhaps greater plasticity for the establishment and validation of cognitive processes in the developing human brain.

It has long been known that lower vertebrates, such as fish and amphibia, possess a remarkable potential for regeneration of different parts of the central nervous system.[9,11] Recovery of certain motor functions following damage to the motor system in immature monkeys is rapid and virtually complete in contrast to similar damage in adult animals, but why this is so has escaped adequate explanation. Whereas previously neuroscientists were busy detailing the reasons why brain neurons could not regenerate or sprout new axons and synapses, they are now recording all the conditions in which axonal sprouting and new synapses can be achieved. The question is no longer, "Why don't mammalian central neurons regenerate axons and synapses?" but rather, "What are the factors preventing axonal regrowth after injury?" The turnabout in conceptualization augurs well for mental retardation research. Advantage must be taken of every opportunity to disclose the factors preventing or restricting synaptogenesis and regeneration of damaged axons if, as is currently suspected, some forms of mental retardation are associated with faulty synaptogenesis.[6,12]

The problem of brain modifiability is not exclusively a problem of damaged axons sprouting new collaterals and synapses. For example, recovery from frontal cortex lesions in infant monkeys is associated with new connections that form between intact cortex and certain subcortical structures. It has also been shown that training infant monkeys before they sustain frontal cortical lesions can greatly facilitate recovery of functions involving the damaged cortex.[5] Here behavior is in some fashion facilitating mechanisms of functional recovery. Whereas the neurobiological dogma was once, "Neurons make synapses and synapses make behavior," now it may have to be added that "behavior modifies synapses." Are there "motivational" systems that employ the vast biogenic amine and peptidergic projection pathways of the neuraxis that are capable of facilitating (or restricting) synaptogenesis and recovery of function? Clearly, every avenue of approach dealing with the cellular and integrative neurobiology of restitution and modification of brain function should receive attention in mental retardation research.

Genetics and Metabolism

It has been clear for some time that metabolic disturbances represent a major etiologic basis for mental retardation. Such disturbances may result from inherited diseases of metabolism, exposure to toxic substances--either in utero or postnatally--or nutritional inadequacies. Genetic research related to mental retardation has produced a number of dramatic developments during the past 20 years. Some of the high points of this period included recognition of the role of chromosome disorders, development of screening programs for PKU, prevention of mental retardation in PKU by dietary management, and the recognition of the role of lysosomal enzyme deficiencies in the causation of mental retardation.[20]

There has been significant progress in understanding genetically determined metabolic abnormalities. The detailed biochemistry of numerous inherited diseases has been elucidated, resulting not only in increased basic understanding, but also in important advances in both treatment and prevention. To a considerable extent, the research progress has resulted in improved methodology, especially the use of tissue culture techniques and the many advances in basic biochemistry. It has been particularly exciting and rewarding to apply the new knowledge to the study of human disease. This process has been facilitated by the training of increased numbers of investigators who are at once knowledgeable in modern biology and biochemistry, and committed to the study and treatment of human disease.

The detailed elucidation of the metabolic basis of inherited disease has had the following direct applications to the control of mental retardation and related disabilities:[21]

- Methods of screening newborns for specific diseases. Such screening programs are now performed routinely, particularly for those diseases that are subject to treatment. As a result of such programs, mental retardation due to PKU is regularly prevented.

- Methods of diagnosing other rarer syndromes. Although applied on the basis of suspicion, such methods have permitted rational treatment of many patients.

- Accurate diagnosis of certain diseases that are not yet treatable. This permits counseling of families regarding risks for future pregnancies.

- Methods for prenatal diagnosis of many diseases.[21]

Within the past 2 years, new methods have been developed for analyzing the gene structure, and they permit diagnosis of genetic disease in cultured cells that do not exhibit the metabolic defect. These methods, based on the use of recombinant deoxyribonucleic acid (DNA) technology, should help refine and extend the usefulness of prenatal diagnosis.

The extent of retardation caused by intrauterine or postnatal exposure to toxins or drugs is not as yet clear. The effect of lead ingestion has been known for a long time, and measures to decrease exposure to high concentrations of lead have resulted in a dramatic decrease in lead encephalopathy in children. It remains to be determined whether exposure to lower concentrations of lead present in the environment of an industrial society results in more subtle impairment of mental ability. It has clearly been established that other factors, such as alcohol ingestion during pregnancies, may have devastating effects on the developing fetus. Concern has also been expressed about the effects of moderate to heavy maternal smoking on fetal development. The effect of nutrition on development of the brain during pregnancy and the neonatal period is under continuing investigation. There is little question that severe malnutrition leads to marked impairment of brain development and subsequent defective mentation.[13] What is not as clear is the effect of more subtle dietary deficiencies. Of particular interest is the possible relationship of dietary restriction to individual requirements based on genetic makeup.

A major cause of mental retardation is defective in utero development. Many factors influence the complex processes involved in the transformation of the fertilized egg into an infant, and the elucidation of the nature of the differentiation process is one of the most intriguing and profound challenges to modern biology. The recent explosion of knowledge concerning cellular and molecular biology has opened up the possibility of a new level of understanding of fetal development.

The accomplishments of the past several decades seem meager, however, compared to the potential offered by recently developed biological tools, especially recombinant DNA. The information that will be provided by recombinant DNA and the technologies that will be based upon it are certain to be so momentous that the influence of this tool will change dramatically all of genetics research. The lack of knowledge that has blocked an understanding of mental retardation ensures that research in this area will benefit particularly from the insights promised by recombinant DNA. Although the very magnitude of the anticipated developments precludes the accuracy of any forecast, some general areas of expectation seem sufficiently certain to make their description worthwhile.

It is already possible to isolate any gene whose function is well understood at a biochemical level. At the most, only time and effort are needed to make use of this knowledge, since the techniques are available and thoroughly tested. When the location of the gene on the human chromosome has been determined, the most recent advances, which are not yet published, permit the isolation of genes whose function is not known, although the disease they cause may be familiar. Even when the location is not yet known, these new tools will provide the means to obtain this information. Difficult as it is to believe, the genetic defect that underlies each form of inherited mental retardation may soon be definable. Much more fundamental genetic research must be carried out in the next 5 years, however, before such genetic defects can be investigated with recombinant-DNA methods.

Translating the dramatic prospects of genetic research into actual research will require money, personnel, and time. The most serious problem may be the difficulty in avoiding undue delay in transferring the new techniques and new knowledge, both to researchers and to the clinicians who are to apply their findings to patients. Individuals who completed their training 5 or more years ago probably did not receive the necessary instruction to take full advantage of the new technology. While this will be true for both researchers and clinicians, catching up will be even more difficult for the clinician, whose education necessarily included less emphasis on the basic sciences. Extensive educational efforts will be required to enable clinicians to use the new diagnostic and therapeutic tools that will be thrust upon the medical world.

Research to date clearly points to certain important directions for the future. Some of these are as follows:

- Continue study of already defined heritable diseases that result in mental retardation to: better understand metabolic pathways and permit improved diagnosis and new strategies for treatment; define new syndromes that may have a metabolic basis; elucidate the mechanism by which metabolic diseases affect developmental processes in the brain and cause mental retardation; and improve diagnostic methods to assure greater accuracy, specificity, and simplicity.

- Expand studies on methods of genome analysis, so that diagnosis can be accomplished on readily available cells. The methods that have been developed for the study of hemoglobinopathies should be applicable to a wide variety of genetic diseases. Such methods would be particularly valuable for the

study of diseases such as PKU which cannot be carried out in readily available cells. This approach involves recently developed methods of molecular biology that can now be applied to the study of mental retardation.

- Expand research in the area of developmental biology. It seems likely that the exciting progress made in understanding the control of gene expression in nucleated cells should soon be applicable to a more general study of the normal process of differentiation and the factors that interfere with orderly progression in normal development.

- Continue research, including clinical observation, on the effects of environmental pollution and drugs on the developing fetus.

- Continue research on the role of nutrition in brain development.[13] Although such research is difficult to carry out, the possible role of genetic variation in determining the effect of nutrition is of great importance. Efforts should be encouraged on the development of animal models for such studies.

Behavioral and Social Aspects

Behavioral and social scientists focus on various components of human intelligence to determine clues that are seminal to its growth and those that are irrelevant or of lesser importance.[22-24] Deviant developmental processes are charted that contribute to mental retardation, together with the social forces that affect the retarded. The search is designed both to illuminate knowledge of normal developmental processes and to find methods to ameliorate or eliminate retardation itself.

During this century, scientists and educators in the field of mental retardation have worked and continue to work with a number of threshold questions including: the plasticity of intelligence; the nature of social adaptation of the retarded; the social impact upon the family of the retarded individual; and why processes such as memory, attention, and learning seem distorted in the mentally retarded individual.

In the past two decades, research and research training in the behavioral and social sciences concerning mental retardation has expanded dramatically through increased resources provided by Federal agencies,[25] such as the

National Institute of Child Health and Human Development, the National Institute of Mental Health, and the Bureau of Education for the Handicapped in the U.S. Office of Education. In general, the following areas of research have been pursued:

- Methods to modify the slow developmental rate of the mentally retarded child through various intervention programs and stimulation procedures;[26,27]
- Descriptions of the developmental processes at the heart of learning, intelligence, and social adaptation of the retarded individual;
- Identifications of interrelationships of biological and behavioral factors that seem to mesh and influence the development of the retarded child and adult; and
- Influences of a variety of social factors in the environment--from families, to neighborhoods and schools, to subcultural attitudes and values--on the adaptation of the retarded youth and adult.

Plasticity of Measured Intelligence

During the past two decades questions concerning the relative influence of heredity and environment upon human intelligence in general and mental retardation in particular have been clarified and enlarged.[28] The subject has always been complicated by the clearly polygenic* nature of the hereditary component of mild retardation, which shows no apparent neuropathology, and by the limitations of the tools used to measure human intelligence. The vast majority of individuals labeled mentally retarded are in the "mildly retarded" category (75-90 percent), and most of them do not have neuropathological conditions identifiable by current methods or technologies. An issue of the potential modifiability of measured intelligence therefore arises, and it has substantial social and educational implications.

Two basic sets of studies have been designed to address this topic. One set has tried to show modifications in existing patterns of behavior by interventions with child and parent at an early point in the child's development.[29]

*In several rare-incidence conditions, such as tuberous sclerosis or phenylketonuria, a single gene or gene pair has been identified as a causal factor.

The interventions have focused on the stimulation of language development, intersensory integration, and the development of more effective social patterns of response. Studies in the second set have focused on intervention efforts around larger social modifications, such as foster care, adoption, or income maintenance experiments. These efforts have proceeded on the assumption that the larger social milieu is the more influential in inhibiting normal development, and that attempts to change the individual without changing the social environment in which he or she exists produce limited improvement.[30]

Studies of the direct intervention strategy make some summary statements possible. An average gain of from one-half to one standard deviation--7 to 15 IQ points--has been revealed in developmental growth rate in young children. The gain of children with mild mental retardation is below average for their rate of development and in comparison with children of their own chronological age, but they have greater potential to perform adequately in educational and vocational programs. Although followup studies reveal subsequent loss of at least some of the IQ gains, they also show a continuation of more efficient school performance than has been noted in comparison children.

Fewer systematic intervention efforts have been made with moderately to severely handicapped children, but some of them have been instructive. Among subgroups with identifiable pathologies, one of the largest consists of children with Down syndrome. Early clinical wisdom regarding Down syndrome held an expectation of a life of semidependence and a developmental rate less than half that of the normal child. Intensive early intervention has raised hopes for a much improved prospect for a few Down syndrome adults, some of whom can possibly operate at a self-sufficient level, while others can be advanced in adaptation considerably beyond the level expected earlier. Studies in this area have revealed that the real limits of development for the mentally retarded can be identified only through intensive efforts to provide maximum, positive conditions for growth and through observations of how an individual responds to those efforts.

Developmental Processes

Research programs concerning the mentally retarded child and adult have focused on the questions of why and in what specific manner the retarded respond inadequately to the world around them. While it is difficult to separate such processes as memory, attention, learning, and language

from one another in the functioning human being, researchers have found it useful to focus on each separately, and they have advanced the understanding of the processes despite two limitations: (1) the etiology of the subject population often was not given sufficient importance, and retarded individuals with moderate to severe pathological conditions were mixed with presumably neurologically intact children and adults; and (2) subjects were asked to respond to laboratory tasks or games that were so carefully controlled as to be far from real life situations or problems.[31,32]

Memory

One aspect of learning is memory, which consists of the ability to perceive relevant events, place them in storage, and withdraw them upon demand in relevant situations. One key step in this process is the transfer of material from short-term memory to long-term memory. It is a step facilitated by rehearsal, which is a type of internal review of relevant material that increases the likelihood of recall. Most retarded individuals reveal demonstrable deficits in the rehearsal process, as well as in each step in the memory process itself. It is called by some the "everything" deficit. At the same time, generalizations about group tendencies do not necessarily apply to a particular retarded child. Research suggests that mentally retarded individuals have problems that relate to storage of relevant information because of attentional difficulties, transfer of learned information from short-term to long-term memory, linkage of recently acquired information to previously stored information in ways that facilitate recall, and use of overall strategies that can aid in memory recall.

In fact, memory deficits for mentally retarded individuals may be worse than what is revealed by the existing research literature since the vast majority of studies have been conducted in a controlled laboratory-like setting. In the social environment of the classroom or neighborhood, with its many distractions and competing stimuli, the mentally retarded individual who has to use this defective process may be at a greater disadvantage than was previously thought.

Attention

The ability to maintain a focus upon material to be learned is obviously of key developmental importance. The ability to attend to relevant details, to sustain attention

over a continuous period of time, and to resist distraction from competing stimuli are all fundamental components of attention. Underlying elements are the nature of the stimulus in a given situation, the ability on request to transfer attention to other relevant stimuli, the novelty of the stimuli themselves, and the presence of rewards for performance. An extensive body of literature suggests that the mentally retarded individual may have difficulty in making visual discriminations because of an inability to perceive key elements. In addition, what was sometimes presumed to have been a deficit in memory may have been a difficulty in maintaining attention.[33]

Mentally retarded children and adults with identifiable brain injury have been noted to have such observable defects as distractibility, hyperactivity, and problems of visual orientation, which suggest a disruption of overall control mechanisms that normally inhibit random movements and make selective and sustained attention possible. Even in these instances, systematic training can help provide some compensation for the disruption.[34]

Learning

The ability of a mentally retarded individual to learn--that is, to use experience to modify behavior--is intimately interwoven with the previously noted processes of attention and memory. A variety of researchers have tried to identify the nature of learning deficits in mentally retarded children and adults. This goal has been approached mainly through the device of presenting a variety of laboratory tasks having clearly defined stimuli and limited choices of a response so as to reveal the deficit more directly. Such research has revealed the following strong tendencies:

- The mentally retarded do not respond to cues that would help solve problems;
- They do not attend to the relevant dimensions of a problem; and
- They do not use active strategies by which they might organize information and attack a problem.

Although training on a particular problem has been shown to be useful in improving the retarded individual's performance on <u>that</u> problem, little progress has been made in effectively transferring training from one problem to a related one. On the other hand, recent attempts to teach

problem-solving strategies to mentally retarded individuals so that they might effectively solve a wide variety of similar problems have shown promise, and they should be continued.

Other investigations have sought to discover effective ways to help moderately and severely handicapped children exercise self-care, adapt socially, and attain partial economic self-sufficiency.[35] A large body of research carried out in many different settings in the last 20 years has demonstrated that all but a very few severely retarded persons can be taught some communication skills, self-care skills, and primitive work skills. With supervision, many can manage their own daily lives and can function in sheltered work settings.

The application of the principles of behavior modification to moderately and profoundly retarded individuals has shown that self-care and partial economic self-sufficiency are realistic societal objectives. Applications of the concept of operant conditioning have been wide-ranging and include adaptations in hearing assessment for the multiple-handicapped, the teaching of nonvocal symbolic language, the teaching of constructive social behaviors, and the reduction of self-injurious behaviors. Such techniques developed for use with retarded individuals have been applied subsequently with success to autistic, aphasic, and psychotic children and adults.

Language

The mastery of language has become one of the key signs of competence in modern society. Researchers have questioned whether language acquisition in the mentally retarded is simply delayed, or whether there are qualitative differences as well. The answer appears to vary with different types and levels of retardation. The mildly retarded child without obvious pathology is generally characterized by linguistic delay, whereas the moderately and severely retarded exhibit more complex linguistic difficulties.

A strong trend in language research is to move away from static measures of language as represented by responses to vocabulary items on intelligence tests, although there is still interest in word meaning and concept formation in the retarded. A new interest has emerged in the field of pragmatics--the study of language usage in natural settings. Language training programs are increasingly designed to simulate naturally occurring language, which requires the instructor to understand the ways that infants and small

children socialize, communicate with others, process information, learn words, and perceive the world.[36]

This approach calls for the study of natural language acquisition. By examining linguistic patterns between parents and children, research has shown that middle-income mothers have more verbal interchange with their child, stress causal relations more ("if you touch the stove, you will burn your hand"), and place less stress on the use of language to direct or control behavior than do low-income mothers. If the approach of pragmatics is correct, different patterns of parent-child interactions can have significant long-term effects on language development and usage. Deficits in language development seem to be reversible, in part, through parent or parent-surrogate training.

A different approach has been taken with children who are moderately to severely retarded and are essentially unable to use the traditional oral-aural-visual system. By combining the techniques of operant conditioning with nonverbal modes, such as sign language, and special code systems designed to augment communication, it is possible to establish social and functional communication and lay the groundwork for further education.

Social and Personality Development

The increasing attention paid to social adaptability of the retarded individual, including the societal goals of "mainstreaming" and placement of children in the least restrictive environment, has focused attention on special problems of social and personality development. An extensive literature has been available for some time identifying personality factors, such as cooperative attitude, persistence, and absence of hostility, as critical for predicting social or vocational success for retarded adults. The inability of retarded individuals to discriminate relevant from irrelevant cues and to pay attention causes some social problems. Research has focused on the effects that a lack of social competence and failure have on the retarded individual. A growing body of literature suggests that the retarded individual:

- Evinces greater levels of anxiety, which tend to be debilitating in a learning setting;
- Tends to be outerdirected, to distrust his/her own abilities, and to look to others for solutions; and
- Tends to be more passive and conforming.

Since these characteristics obstruct reaching the goal of social competence or adaptability, attention is now being focused on ways to design environments that will increase motivation and reinforce constructive behavior patterns in the retarded individual.[37] If meaningful and challenging success experiences are arranged for the retarded, positive responses appear similar to those that occur in the normal child.

A new avenue of research explores the organization of services for the moderately and severely retarded, through group homes, institutions, and other care settings. Recent studies reveal a growing awareness of the importance of the social milieu for the adaptation of the individual retarded citizen. Attention has therefore been directed to the question of restrictiveness of institutional environments.[38] The occurrence of "burnout," a term used to describe the reactions of staff members or parents who daily interact with the retarded, is another influence that has a negative effect on the retarded child's development.

Biology-Behavior Interaction

Recent research has sparked renewed interest on questions of the interaction of biological factors with social and behavioral factors. Several studies have revealed a complex interrelation between complications at birth, retarded development, and socioeconomic class. Retardation as a consequence of birth complication appears to be more prevalent in children from low-income families than in those from middle-income families even when comparable complications are present. Furthermore, there appears to be a linkage between an environment of poverty, increased incidence of postnatal biological insult, and possible behavioral consequences. Children in low-income environments are more likely to suffer from lead poisoning and from herpes. Such disorders can have severe negative behavioral consequences for the child.[39,40] The search for relevant interactions of biology and behavior have intensified in the past decade and will likely play an important research role in the future.

Toward a New Definition of Mental Retardation

The accumulation of research on cognition, social adaptation, and biobehavioral interactions has led to a modification of the definition of mental retardation.

Earlier definitions stressed the constitutional nature of retardation and the essential permanence of the condition. For the mildly retarded individual, there is a greater recognition that the condition can be a social systems issue as well as a clinical problem.

In the definition currently in use, mental retardation refers to significantly subaverage general intellectual functioning, existing concurrently with deficits in adaptive behavior, and manifested during the developmental period. It tends to emphasize social factors, although it falls short of the distinction drawn in table 1.

Such a definition implies that in one locale a child can be looked upon as mentally retarded but that in another, where the demands on adaptive behavior are different, he would be looked upon as normal. This notion is very different from the one that holds retardation as "constitutional."

In summary, the last two decades of research in the behavioral and social dimensions of mental retardation have influenced practically every aspect of the retarded individual's life. This research has:

- Examined the plastic nature of intelligence and encouraged hope for limited, but socially significant, modification of cognitive and linguistic abilities;
- Investigated the interaction of social forces with the retarded person and focused attention on the adaptive potential of the retarded;
- Demonstrated the potential for increased understanding and improvement of memory, attention, language, and learning skills;
- Reinforced the importance of the preschool period for the beginning of systematic training;
- Reintroduced the concept of a complex interrelationship between the biological constitution and the social ecology of the retarded individual;
- Emphasized the importance of personality and behavior patterns underlying the adaptive potential of the retarded adult; and
- Enlarged and clarified the definition of mental retardation.

TABLE 1. Social and Clinical Definitions of Retardation

Social	Clinical
Mental retardation is an achieved status in a social system and is the role played by a person with that status.	Mental retardation is an individual pathology that can be diagnosed using medical-pathological and(or) statistical models of "normal."
Mental retardation is specific to a social system. A person can be retarded in one place and not in another, depending on whether the person is labeled by the system.	Mental retardation is a characteristic that transcends cultures and sociocultural groupings. A person either is or is not mentally retarded.
The prevalence rate for mental retardation will be relative to the content focus, level formation, and tolerance limits of the norms of a particular social system, and to the extent to which the status of mental retardate is differentiated within the structure.	The "real" prevalence rate for mental retardation can be determined without regard for the norms of a particular social system, given adequate research design and instruments.

Source: Adapted from Mercer, J.: The myth of 3% prevalence. In Eyman, R., Meyers, C., and Tarjan, G. (Eds.): Sociobehavioral Studies in Mental Retardation: Papers in Honor of Harvey F. Dingman. American Association of Mental Deficiency, Monograph No. 1, 1973, 1-18.

Important Questions

There is a direct relationship between important needed research and the research accomplishments of the immediate past. Programs of research represent concepts that bridge the past and future, and research investments that have been productive in the past carry expectations of future promise.

Life Span and Life Transition

There has been a growing realization that special problems are different for different age levels of the mentally retarded.[41] The problems of the 3-year-old, for instance, are not those of the 10-year-old, and certainly not those of the adult who is labeled retarded. Social adaptation problems can be solved at one age without necessarily compensating for problems that may emerge at a later age. Figures on the prevalence of a given problem at a given age level raise questions not yet answered. Accordingly, a need has been recognized for studies that follow retarded individuals over a significant period of their life span, or at least over those identifiable transition points between stages, to view the changes that take place. It has become apparent[42] that there may be many intellectually subnormal individuals who are never institutionalized and who are never brought to the attention of social agencies. Little is known of their life-span processes.

One of the least studied transition points occurs when the retarded individual leaves the public school programs or the institution and enters the work force or community. What are the special conditions in society that influence adaptation? What cognitive learning and social factors predict favorable or unfavorable community adjustment? These are all questions that can be answered by careful tracing and sequential observation of the individual, his or her family, and his or her interactions with various social institutions. Tracing over a lifetime the probable causes of retardation and the progressive evolution of individuals with different characteristics will reveal knowledge about the mentally retarded in society. In particular, there may be different developmental life span patterns for children with Down syndrome, mildly retarded children, and children with PKU.

Much more information is needed on the conditions that lead to an increase in the frequency of mental retardation and those that lead to a decrease. Large longitudinal studies, such as the Collaborative Perinatal Study, have gone largely unmined in terms of their potential for yielding information on the incidence and prevalence of various types of mental retardation.

The present movement toward deinstitutionalization and the probable future trend in which individuals who once would have been institutionalized remain instead in their communities intensify the need for a solid base of life-span information on the physical, social, and cognitive growth and development of the mentally retarded.

Cognitive Training

Work done mainly in the laboratory on cognitive processes such as attention, memory, learning, and language has laid the groundwork for the possible design of systematic programs of instruction to enhance these developmental processes in the retarded individual. Attempts to train mentally retarded individuals in the mastery of long-lasting cognitive strategies also fit into these general research objectives. The ability to train mentally retarded children and adolescents to learn specific cognitive strategies has already been demonstrated to some extent; the next question is whether such training can be generalized or transferred to other tasks and situations. Additional work is needed to bring currently developing theories of attention and memory to completion and to test their applicability outside the laboratory.

One of the most elusive goals for the mentally retarded individual has been the transfer of training, and it opens the question of social adaptation. Must the retarded be trained anew for each new task? Can they be trained to choose wisely among alternatives, not only in the laboratory or the classroom, but in the community where proper choices are critical? One challenge to current researchers is to move beyond observation and controlled laboratory experimentation to demonstrations of systematic and predictable changes in cognitive processes in the natural environments in which skills are to be used.

Language training represents another fruitful area of investigation. The growing sophistication on the nature of language and the means by which it is acquired increase the possibility that research can be designed to test the retarded child's and adult's true potential to master certain functional aspects of this key symbol system. The initial attempts to develop alternative modes of communication, as described earlier, have appeared fruitful. The application of these newly devised language augmentation programs, however, has just begun. The design of such linguistic innovations can advance the understanding of communication modes and the means by which language interacts with social and vocational adaptation.

Retardation and the Family

The observation that severely retarded children produce a crisis in the family was made many years ago. Two types of crises are evident. The first is the symbolic death of the parents' wishes, dreams, and aspirations for their child as they gradually come to terms with the fact of retardation. The second is the need to interact daily with a dependent and often difficult child.

Since fewer retarded individuals are automatically institutionalized, the family of the retarded has become an increasingly important topic for research. Clinically, it is suspected that the impact upon the family of caring for the retarded individual changes at various age levels. There has been a shortage of investigations, however, on the progressive influence and impact of the mentally retarded individual on parents, siblings, and the complex network of relationships known as the extended family. The limited research now available on the long-term relationship between the family and a chronically dependent person suggests that this phenomenon needs more attention and that improved methodology needs to be developed. A research initiative focusing on these family relationships will shed light on normal family dynamics and, at the same time, produce an information base for service programs to assist the family.

The sequential impact of family variables upon the retarded child also needs attention. Study is needed on the commonly observed tendency for families to become overprotective and not allow the retarded child to attain a degree of independence within his or her reach.

The number of families that disintegrate in the course of maintaining a retarded member is not documented, nor are the particular sources of strength--personal or support systems--that can be observed in those families that can cope. Also not known are the manner and degree of external social supports that can make a significant difference in family members' adaptations.

The pressures that are faced by the siblings of retarded individuals have been reported in clinical case studies but rarely in systematic investigations. Theoretical models of family life need to be developed and tested in this special situation where the "stressors" of mental retardation create family stress, and where support systems have to be designed to help individuals handle that stress.

Ecology

Some interesting preliminary observations have been made on the complex interaction between the social and

physical environments of the retarded child and adult. The major social movement in the direction of deinstitutionalization raises questions about: (1) the effects of community placement on the development of the mentally retarded; (2) the effects of size of residence and type of programming on the development of the mentally retarded; and (3) the effects of mandating home care of the severely retarded young, in terms of a variety of dimensions of family adjustment.

There is concern that current service practices, while well-meaning, have outrun the knowledge and understanding of the social and organizational problems that are triggered by the philosophies of mainstreaming and normalization. The new designs for independent or semi-independent living require more sophisticated knowledge of social pressures and the responsiveness of the retarded individual to them.[40,43-45]

Biology and Behavior

The range of social conditions that affect children with different biological characteristics may be much larger and more significant than has been thought. The availability of advanced data processing techniques and computer capabilities now allows investigators to pursue such complex interactions in ways not previously possible.

Another relatively new area that seems to have potential is the subdiscipline of behavioral toxicology. It has led to the discovery of a wide range of central nervous system dysfunctions associated with behaviors during pregnancy. Cigarette smoking and moderate-to-heavy alcohol use during pregnancy, for instance, have been associated with impaired learning abilities and developmental lags in offspring as well as with intrauterine growth retardation and increased risk of perinatal complications and death.

As noted previously, the complex of interacting variables occurring in the context of poverty needs to be studied for its potential to produce a variety of types of biological problems relating to mental retardation. The social and behavioral consequences of these biological intrusions represent a new need for interdisciplinary study.

Training in Specific Skills

In an earlier section of this report, the wide variety of contributions made through the application of concepts of behavioral modification and operant conditioning was discussed. An important continuing research area focuses

on the modification of self-destructive and socially disruptive behaviors observed in many severely and profoundly retarded individuals. Most work so far has focused on controlling these behaviors in adults. Studies of the development of these bizarre patterns in infancy, however, might produce a better understanding of their origin and significance and lead to more effective and efficient prevention or amelioration.

III. Priority Areas for Research

Biomedical Research

Neurobiology and Neuroanatomy

- Mechanisms of regulation of neuron number and neuron type. Factors in neurogenesis, development, and differentiation of glia.

- Development of neuron-glia interactions; mechanisms of neuronal migration and establishment of correct locations in brain.

- Development of synapses and mechanisms establishing appropriate synaptic relations; neuron-neuron interaction processes. Identification of cell surface membrane recognition molecules through use of immunological techniques with emphasis on monoclonal antibodies.

- Development and exploitation of cell culture systems for analysis of neurite and synapse formation, cell surface specific receptors, cyclic nucleotide-linked metabolic processes influencing surface membrane properties.

- Mechanisms of programmed cell death, elimination of redundant synaptic connections and processes of synapse "stabilization."

- Development of receptor-ionophore complexes in excitable membranes; their distribution and turnover at synapses and in nonsynaptic electrogenic membrane.

- Ontogenesis of voltage-dependent and voltage-insensitive ion channels at different sites in different neuronal subsystems.

- Mechanisms regulating dendritic and axonal growth and branching patterns. Identification of factors controlling morphology, distribution, and number of dendritic spines. Relationship between dendritic spine morphophysiology and presynaptic elements.

- Role of cytoskeletal constituents (microtubules, neurofilaments) in neuronal geometry and dendritic function.

- Role of neuron growth promoting and regulating trophic factors in neuronal differentiation and expression of synaptic relations.

Neurochemistry and Neuropharmacology

- Development of biosynthesis, transport, release, and reuptake or inactivation processes regulating transmitter/modulator actions of acetylcholine, amino acids, biogenic amines, and peptides with demonstrable effects on neuronal activity.

- Elucidation of the role of these transmitter/modulator agents in the immature brain.

- Developmental biochemistry and morphophysiology of myelin and regulation of axon-glia relations in myelin formation.

- Developmental neurochemistry of bioenergetic mechanisms in neurons and glia; membrane structure and chemistry of glycolipids, glycoproteins, proteolipids, and glycoaminoglycans.

- Molecular and cell biology of lysosomal enzyme disorders and their pathogenetic mechanisms in the developing mammalian brain.

- Analysis of the biochemical pharmacology of projection and interneuronal systems of the immature nervous system.

- Analysis of the changing pharmacological properties of different synaptic subsystems in vivo and in vitro during the developmental process.

Neurophysiology

- Ontogenesis of spontaneous and evoked cortical potentials including event-related potentials in

studies of normal and aberrant neurobehavioral development.

- Studies of neuronal plasticity and factors determining the time course and degree of modifiability of developing neuronal subsystems.

- Development and regulation of blood-brain barrier mechanisms; control of extracellular milieu of immature neurons and glia; factors modifying regional brain capillary permeability.

- Development of peripheral and central sensory subsystems and identification of physiological strategies of information processing at different maturational stages.

- Developmental elaboration of motor behavior; contribution of subcortical, basal ganglia and cerebellar-brain stem subsystems.

- Utilization of neurotoxins, antimetabolites, and surgical ablative procedures to investigate the maturation of different synaptic organizations involved in the operation of motivational systems.

Genetics and Inborn Errors of Metabolism

- Studies on behavioral genetics in invertebrates and laboratory mammals. Role of genetic mechanisms and their modification by experiential factors in behavioral processes.

- Continued definition of new syndromes that may have a metabolic basis.

- Improvement of diagnostic procedures to assure greater accuracy, specificity, and simplicity.

- Expansion of exploration for methods of genome analysis with emphasis on recombinant DNA techniques.

Behavioral and Social Sciences Research

Prevention of Mental Retardation Due to Unknown Causes

- Acquisition of demographic information about questions concerning the mentally retarded.

- Application of data processing techniques to develop knowledge of complex biology-behavior interactions.
- Studies in behavioral toxicology.
- Studies of interacting variables in a poverty environment for their impact upon biological problems relating to mental retardation.

Enhancing Thinking and Learning in Retarded Individuals

- Development and evaluation of programs of instruction to enhance developmental processes.
- Comparative studies of the strategies employed by normal and retarded persons to generalize or transfer learned tasks to other tasks and situations.
- Studies of attention and memory in the retarded.
- Studies of the applications of behavioral modification and operant conditioning techniques in controlling bizarre behavior patterns in severely retarded adults and of the development of these patterns in infancy.

Amelioration of the Effects of Mental Retardation

- Lifespan studies of the mentally retarded.
- Studies of the relationships between the mentally retarded and their environments.
- Investigations into the mechanisms of language and development of alternative modes of communication.

Alternatives to Institutionalization of Retarded Persons

- Studies on the impact of family variables upon the retarded child.
- Studies on the effects of deinstitutionalization in respect to community placement, size of residence, and type of program and home care.

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